aplasia. Cytogenetics revealed trisomy 8 mosaicism, present on a BM specimen obtained pre-GTx (Blood 2007; 109:503). Our 2nd patient enrolled in January 2007. He received 5×10^6 CD34+ cells/kg that showed 40–200U of ADA activity after transduction (normal range 58–128). Over 6 months, this patient showed a slow increase in ALC (up to 750/mcL) and lymphocyte function. PBMC ADA activity has been up to 50U. The dAXP level has decreased to below 10%, levels typically seen after allogeneic BM transplant. A 3rd patient was treated in May 2007 and received 2×10^6 CD34+ cells/kg with ADA activity of 7–87U. Over three months, lymphocyte function has increased over pretreatment level. PBMC ADA activity has been up to 24U and the dAXP levels have decreased to less than 10%. Both patients have been off PEG-ADA since 2 weeks pre-GTx and had mild post-GTx courses, with no documented infection, and no need for blood products. AST and ALT rose to 200 U/L, and then resolved, an effect attributed to PEG-ADA withdrawal or busulfan administration. Without myeloid growth factors, times to neutrophil count above 500/mcL were 36 and 45 days. These data are consistent with the positive results of GTx for ADA-SCID obtained in Milan and London and directly show that PEG-ADA withdrawal and reduced conditioning improve the outcome of GTx for ADA-SCID. Longer follow-up should allow us to study engraftment of cells containing vector-specific sequences and to conclude if either vector contributes more to recovery of lymphoid immunity.

69

SIROLIMUS (SRL)-BASED GVHD PROPHYLAXIS AFTER TBI/TT/CY ALLOGENEIC HSCT IN PEDIATRIC PATIENTS WITH HR ALL: RESULTS OF A MULTI-INSTITUTIONAL PILOT STUDY

Pulsipher, M.A.[1], Wall, D.[2], Goyal, R.[3], Grupp, S.[4], Bunin, N.[4]. [1] University of Utah/Primary Children's Medical Center, Salt Lake City, UT; [2] Methodist Children's Hospital, San Antonio, TX; [3] Children's Hospital of Pittsburgh, Pittsburgh, PA; [4] Children's Hospital of Philadelphia, Philadelphia, PA.

Relapse and NRM after allogeneic HSCT remain significant barriers to success in treating very high-risk ALL. Sirolimus (SRL) has been shown to have cytotoxic activity against human ALL at serum levels used for immune suppression. We hypothesized that the addition of SRL to a tacrolimus (TAC)/methotrexate (MTX) GVHD prophylaxis regimen would decrease relapse after HSCT for ALL. This multi-institutional pilot trial included a preparative regimen of fractionated TBI (1200 cGy), thiotepa (5 mg/kg/d × 2) and cyclophosphamide (60 mg/kg × 2). Pts received IV TAC (start d-2, target 5–10 ng/mL), PO SRL (start d0, target 3–12 ng/mL), and IV MTX (5 mg/m^2, d + 1, +3, and +6 plus d + 11 for UD BM/PBSC). TAC was tapered between d + 42–96 for MSD and d + 100–180 for others. SRL was tapered over 4 wks starting 6 m after transplant. This report includes 50 pediatric pts (med age 9 (1–21)) with a med f/u of 17 m (5–50). Immunophenotypes included 38 B-lineage and 12 T-lineage. Risk groups included 12 pts in high risk (HR) CR1, 5 in HR isolated extramedullary (IEM) relapse, 8 in very early relapsing (VER,<18 m) CR2, 6 in early relapsing (ER, 18–36 m) CR2, 10 with late relapsing (LR, ≥36 m) CR2, and 9 in CR3. Stem cell sources included 22 MSD-BM, 25 UCB, and 3 UD.

Results: 2 yr EFS for the entire cohort was 72% (SE 8.1) and did not differ by stem cell source. 2 yr EFS by risk groups is outlined in the table below, showing better than anticipated survival in all subgroups. Within the HR CR2 subgroups (BM relapse <36 m from diagnosis), T-lineage VER CR2 pts had worse 2 yr EFS compared to B-lineage VER CR2 and B- and T-lineage ER CR2 pts (2 yr EFS 20% vs. 64%, p = 0.057). One recipient of CB failed to engraft and a second relapsed prior to engraftment. All remaining pts engrafted at a median of 21 (13–31), 28 (16–62), and 20 (17–21) days for MSD, CB, and UD, respectively. aGVHD grade II-IV and III-IV occurred in 40 and 21% of patients, while cGVHD occurred in 30%. NRM occurred in 5 patients (10%: 4 CB, 1 MSD). Significant toxicities included VOD (5 pts, reversible in 3, part of fatal MSOF in 2 in the context of bacterial (1) and viral (1) sepsis), non-fatal HUS (2 pts), and non-fatal IPS (1 pt). In summary, SRL-based GVHD prophylaxis after TBI/TT/Cy allogeneic HSCT results in high rates of engraftment, low NRM, and improved 2 yr EFS in every risk group except T-lineage VER in CR2. A phase 3 trial in the COG for ALL patients in CR2 comparing TAC/MTX with TAC/MTX/SRL after TBI/TT/Cy allogeneic HSCT is ongoing.

2 yr EFS by Risk Group

ALL Risk Group	ALL HR CR1	ALL VER CR2	ALL ER CR2	ALL LR CR2	ALL CR3	ALL IEM CR2
2 yr EFS (±SE)	92% (±8)	38% (±17)	60% (±22)	90% (±10)	65% (±17)	100%

70

IMPROVED OUTCOME FOR TRANSPLANTATION OF PEDIATRIC PATIENTS WITH NON-MALIGNANT DISORDERS WITH UNWASHED PLASMA DEPLETED CORD BLOOD (PD CB)

Rosenthal, J.[1], Jaing, T.-H.[2], Chan, L.L.[3], Eames, G.[4], Graham, M.[5], Tan, A.M.[6], Lin, H.P.[7], Nademanee, A.[1], Karanes, C.[1], Wang, B.[8], Chow, T.[8], Tan, P.[9], Gjertson, D.[10], Petz, L.[8], Chow, R.[8,11], Forman, S.[1]. [1] City of Hope National Medical Center, Duarte, CA; [2] Chang Gung University & Children's Hospital, Linkou, Taiwan; [3] University of Malaya Medical Center, Kuala Lumpur, Malaysia; [4] Cook Children's Hospital, Fort Worth, TX; [5] University of Arizona Medical Center, Tucson, AZ; [6] KK Women & Children's Hospital, Singapore; [7] Subang Jaya Medical Center, Malaysia; [8] StemCyte International Cord Blood Center, Arcadia, CA; [9] Mount Elizabeth Hospital, Singapore; [10] UCLA School of Public Health, Los Angeles, CA; [11] StemCyte Taiwan National Medical Center, Linkou, Taiwan.

CB is an attractive source for unrelated transplantation of benign indications because of the potentially better availability for minorities. Since most patients are children, cell dosage is less of a limitation; however, cell dose is still important. We have consistently employed 3 strategies to maximize cell dose - plasma depletion processing without red blood cell reduction, no post-thaw wash (NW), and the use of double cords (2X) when necessary. A retrospective CIBMTR-audited analysis was performed on all 87 pediatric (<50 kg) patients with non-malignant disorders transplanted with 98 PD CB products (15 double cords) at 21 US and 16 international institutions. Weight was used instead of age to emphasize importance of cell dose. The disease breakdowns were: 40 thalassemias, 12 congenital immunodeficiency syndromes, 9 aplastic anemia, 5 Hurler syndrome, 4 osteopetrosis, 2 chronic granulomatous disease, 2 familial hemophagocytosis, 2 Fanconi anemia, 2 inherited metabolic disorders, and 9 for other disorders. Transplant characteristics: median age 4 years (range 0.1–27); median weight 16 kg (range 4–49); male 54%; HLA ABDR matches: 18–6/6; 32–5/6; 30–4/6; 6–3/6, 1–2/6; median pre-freeze TNC dose 9.8×10^7/kg; median post-thaw TNC dose as reported by TC 6.7×10^7/kg; median pre-freeze $CD34_+$ dose 3.5×10^5/kg; transplants outside of U.S.- 54 (62%); non-myeloablative - 13 (15%); 34% post-thaw washed (W) and 66% infused without post-thaw wash (NW) of those with known post-thaw status. Median follow-up time was 220 days (range 8–1,448 days). With no unevaluable cases, cumulative incidence was used to estimate engraftment, acute and chronic graft-versus-host disease (aGvHD and cGvHD), and Kaplan-Meier estimates were used for all other outcome. As shown below, foregoing post-thaw wash improved engraftment, TRM and survival, and significantly reduced extensive cGvHD. This series is unusual in its cell dose, high even for pediatric patients, and shows that unrelated PD CB transplantation can be performed safely and effectively, with outstanding neutrophil (92 ± 9%) and platelet engraftment (85 ± 9%), extensive cGvHD (3 ± 3%), overall (90 ± 4%) and disease-free survival (78 ± 6%) rates achieved when post-thaw wash is not employed, even in a diverse population of pediatric patients with non-malignant disorders.